REMARKS

Claims 21, 23-25 and 50-59 are pending. Claims 22 and 26 are cancelled and claims 53-59 are added herein.

Claim 21 was amended to more correctly describe the present invention. Claims 50-52 were amended to correct antecedent basis. Amended Claim 21 and new claim 54 are supported by originally filed claim 1 and by disclosure at page 1, line 20, to page 2, line 9, of the specification. New claim 53 is supported by originally filed claim 20 and by disclosure at page 35, lines 1-27, of the specification. New claims 54-59 are supported by originally-filed claims 12, and 16-20 as well as disclosure at page 2, lines 4-26, of the specification.

No new matter has been added by this amendment.

35 U.S.C. § 103

Claims 20-25 and 50-52 were rejected for obviousness over Nishimura et al. in view of de la Monte et al. Claims 20, 22, and 26 have been canceled. On page 5, lines 4-11, of Paper No. 13, the Examiner states:

[I]t would have been obvious to the ordinary artisan to administer an adenovirus vector as taught by Nishimura, where a DNA sequence encoding AD7c-NTP, as taught by de la Monte, had been substituted for a DNA sequence encoding APP 695, injection the adenovirus into the hippocampal region of a rat's brain to observe the effects of AD7c-NTP over expression. Motivation is given by both Nishimura and de la Monte. Nishimura states that over expression of APP 695 resulted in neuronal degeneration in situ, and de la Monte states that over expression of AD7c-NTP in neuronal cells in culture resulted in death of the cells.

The claims have been amended to require a composition containing an exogenous AD7c-NTP nucleic acid, histone, and amphipathic compound. Nishimura et al. fail to describe an animal model, which contains an exogenous nucleic acid, histone, and amphipathic compound.

Nishimura et al. describe administration of APP695 cDNA with hypotonic mannitol; these researchers used hypotonic mannitol to improve the efficiency of gene transfer (see abstract and page 2389, col. 1, paragraph 3 of Nishimura et al.). However, the Nishimura paper fails to describe or suggest a composition containing a nucleic acid, histone, and amphipathic compound. Nor does the combination of the Nishimura and de la Monte.

With respect to gene expression, the Examiner stated:

> As for the limitation that the animal expresses an exogenous Ad7c-NTP polypeptide in a neuronal cell for at least 48 hours, it is taken that expression found at 5 days indicates expression for at least 48 hours. The PTO has no means to perform such tests, and thus applicant must argue or provide evidence that the expression demonstrated in the prior art was not at least 48 hours. (page 5, lines 16-20, of Paper No. 13)

The claims have also been amended to require that the gene expression in neuronal tissue of the model animal be detected at least 4 weeks after administration of the nucleic acid-containing composition, whereas Nishimura et al. reported loss of gene expression in neuronal tissues at approximately day 15. Nishimura et al. describe measuring expression of the APP695 gene on days 5, 10, 15, 20, and 30. These researchers found that APP-accumulating neurons disappeared in one portion of the brain (hilus) at approximately 15 days and detected only weakly APP-immunoreactive cells in another portion of the brain (dentate gyrus) on day 15. In contrast, the claimed animal model is characterized by consistent, long-term heterologous gene expression for at least 4 weeks (and even for 2 months and longer). Such prolonged gene expression has not

been previously achieved. Neither Nishimura et al. nor De la Monte et al. described or suggest the duration of AD7c-NTP gene expression now required by the amended claims. As is disclosed in the specification of the present application, the long-term expression of exogenous nucleic acids in neuronal tissues was surprising (page 12, lines 8-9, of the specification.).

None of the prior art references cited describe or suggest all of the limitations of the amended claims. Moreover, given the unexpected and unprecedented duration of gene expression achieved in the claimed animal model, this rejection should be withdrawn.

35 U.S.C. § 112

Claims 20-26 and 50-52 were rejected for overbreadth. On page 2, lines 10-17, the Examiner states:

> [the claims], while being enabling for rats which have been administered directly into their brain an exogenous DNA sequence encoding AD7c-NTP operatively linked to a promoter in association with a histone and a liposome, wherein expression of said DNA sequence in neuronal cells of the rat results in neuronal cell death, and methods of using these rats in methods of assay to determine compounds which decrease neuronal cell death, inhibit the expression of APP and inhibits the production of plaques in the brains of rats does not reasonably provide enablement for any non-transgenic model for Alzheimer's Disease and methods of using the models.

As is discussed above, the claims have been amended to require a composition containing an exogenous AD7c-NTP nucleic acid, histone, and amphipathic compound. The claims were also amended to require gene expression for at least 4 weeks. The composition contains a nucleic acid as well as "vehicle" components. The mixture now required by the claims is critical to achieving the duration of gene expression specified by the amended claims.

With respect to the composition used in the claimed animal model, the Examiner states (at page 3, lines 10-14, of Paper No. 13):

> It is not possible for the examiner to determine if the use of a vehicle, such as liposome and histone complex was essential to making the claimed model. [H] owever, Nishimura

states that adenovirus alone would not cross the blood brain barrier until the adenovirus was in a hypotonic solution (page 2394, col. 2, lines 10-20).

The histone and amphipathic compounds that accompany the nucleic acid in the composition required by the claim is indeed critical to achieving prolonged expression of AD7c-NTP and development of pathologic features that mimic human disease. Difficulties in achieving lengthy exogenous gene expression in neuronal tissue and associated development of pathologic features consistent with clinical development Alzheimer's Disease are well known in the art.

The Examiner relied on Games and Podlisny in support of the enablement rejection, citing failure to achieve development of Alzheimer's pathologies. Applicants submit that the failure of these researchers is not relevant to the claimed invention, because Games and Podlisny administered peptides, rather than nucleic acids as claimed.

In fact, Nishimura et al. (discussed above) described such difficulties and overcame them to a certain degree. However, Nishimura et al. could not attain the long-term gene expression demonstrated by Applicants. Although Nishimura et al. found that administration of nucleic acids with a hypotonic mannitol solution improved the gene transfer and uptake by neuronal tissue, these researchers found that expression fell off at approximately 15 days post-administration. Applicants have developed compositions and methods, which are surprisingly more effective than previous attempts (such as those of Nishimura et al.) in overcoming the obstacles of earlier methods and have produced an animal model for Alzheimer's Disease, which is characterized by prolonged (at least 4 weeks and longer) gene expression. Prolonged gene expression leads to development of many of the hallmark symptoms indicative of clinical Alzheimer's Disease.

Applicants therefore submit that the amended claims are commensurate in scope with the disclosure provided in the originally filed specification and that the methods described predictably and reliably produce the claimed model for Alzheimer's Disease. Withdrawal of this rejection is respectfully requested.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicant respectfully submits that the pending claims are in condition for allowance.

The Commissioner is hereby authorized to charge any required fees, or credit any overpayment, to Deposit Account No. 50-0311 (Reference No. 21486-047).

Respectfully submitted,

Ingrid A. Beattie, Reg. No. 42,306
Attorney for Applicant
c/o MINTZ LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel.: (617) 542 6000
Fax: (617) 542-2241